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Epirubicin, Methotrexate and Bleomycin in the Management of Recurrent Squamous Cell Head and Neck Cancer. A GSTTC Randomised Phase II Study

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53 patients with squamous cell carcinoma of the head and neck recurrent after initial treatment were entered into a phase II trial of the epirubicin, methotrexate and bleomycin (EMB) combination. The primary objective of the study was to evaluate the activity of this combination. Compliance to EMB and the possible non-cross-resistance to previous cisplatin-containing chemotherapy were secondary objectives. In order to avoid patient selection bias, the study involved randomisation between EMB and a cisplatin–methotrexate–bleomycin (DMB) combination (with EMB: DMB = 2:1). 23 out of 53 (43% ± 13) EMB patients showed an objective response, lasting a median of 12 (range 4–39) weeks; interestingly, 5 out of 14 (36% ± 25) patients pretreated with cisplatin plus 5-fluorouracil responded to EMB. The treatment compliance was good and a median of three courses was delivered. No patient refused the treatment after the initial cycle. Leukopenia (47%) and oral mucositis (42%) were the main side effects. DMB produced a response rate of 33% ± 18 with a median duration of 5 (4–13) weeks. None of the patients previously treated with cisplatin plus 5-fluorouracil responded. 5 patients refused the treatment after the first cycle and a median of two cycles (0–5) was delivered. In conclusion, EMB produced results similar to cisplatin-containing regimens, with a mild to moderate toxicity and a good compliance; the possible non cross-resistance with cisplatin plus 5-fluorouracil deserves further evaluation.
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INTRODUCTION

PATIENTS WITH recurrent cancer of the head and neck pose strong challenges to the medical oncologist. Problems of follow-up, emotional and social factors, cost of treatment, need for admission and duration of hospital stay represent important issues affecting the feasibility of chemotherapy [1].

More active general support to maintain nutrition, pain relief, and open airways, should be used as well as more effective and less toxic chemotherapy combinations for a good palliation.

Over the past 10–15 years, several phase II trials have evaluated combinations of active single agents in patients with advanced/recurrent disease, the best results having been obtained by using cisplatin-based regimens [2].

The cisplatin–methotrexate–bleomycin (DMB) combination has shown a significant therapeutic advantage in terms of response rate over single agent methotrexate in a randomised phase III study [3, 4].

Even if DMB did not show a major impact on survival it showed a superior response rate with a doubling of complete response rate (19%) and may be considered as an appropriate multiple agent regimen.

In 1986, we started a randomised study of cisplatin–5-fluorouracil (DDP-5FU) plus loco-regional treatment versus loco-regional treatment alone [5]. Searching for a new active combination for recurrent patients (inclusive of those resistant to, or relapsing after, DDP-5FU), we conducted a phase II trial of the epirubicin–methotrexate–bleomycin (EMB) regimen, having DMB as control arm. The goals of this trial were: (a) to evaluate the overall response rate to the EMB regimen; (b) to evaluate its toxicity with special regard to compliance and modifications of Karnofsky performance status (KPS).

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MATERIALS AND METHODS

Patient selection

To be eligible for the trial, patients had to have histologically proven squamous cell head and neck cancer. Patients relapsing after a complete response obtained with the first line treatment were required to have a new biopsy or a fine needle aspiration.

Patients aged 75 years or more, having a KPS of 50 or less, or when abnormal hepatic functions were present (elevated serum bilirubin or hepatic enzymes), renal (serum creatinine > 1.2 mg/dl), or bone marrow (haemoglobin < 12 g/dl, white blood cell count < 4000/mm^3, platelet count < 150000/mm^3) were excluded from the study.

In addition, patients with other prior malignancies were excluded. Before entering the study, informed consent was obtained from all the patients, according to local policies. Although no written consent was required it included full information about patient prognosis and about the experimental nature of the treatment.

The study was approved by the GSTTC Review Board and by the Ethical Committee of Centro Oncologico Regionale of Padua.

Study design

The proportion of EMB treated patients whose tumours shrink by at least 50% was the primary endpoint of this study.

A two-stage accrual design first described by Simon [6] was employed. We tested the null hypothesis that the true response probability was less than 20% ("uninteresting" response level) and the alternative hypothesis that the true response probability was at least 35% ("desirable" target level), with alpha error = 5% and beta error = 10%.

We planned: (a) to terminate the experiment at the end of a first, 37-patient, series and reject the EMB combination if eight or fewer responses had been observed; (b) to reject the combination at the end of the second, 83-patient, stage if 22 or fewer responses had been observed.

A two to one randomisation scheme (that is, 2 patients randomised to the new combination for each patient to the control treatment), as first suggested by Peto [7], was used. This randomisation insures that the majority of patients are treated with the EMB combination, thereby providing the greatest information on the endpoint of the study.

Patients were stratified before randomisation for prior therapy (previous induction chemotherapy with DDP-5FU versus no previous chemotherapy), type of recurrent disease (no response or early relapse to initial treatment versus late—> 3 months from remission—relapse), and institution.

Treatment

Patients were randomised to receive: (1) EMB regimen (A-arm): epirubicin (Farmorubicina, Farmitalia Carlo Erba) 50 mg/m^2 intravenously (i.v.) on day 1; methotrexate 40 mg/m^2 intramuscularly (i.m.) on days 11, 18; bleomycin 10 mg/m^2 i.m. on days 4, 11, 18; (2) DMB regimen (B-arm): cisplatin 50 mg/m^2 i.v. on day 1; methotrexate and bleomycin as described for arm A.

The chemotherapy course was repeated from day 22.

Treatment was discontinued if there was evidence of disease progression or intolerable toxicity. When tolerable but limiting toxicity occurred, the administration of the following course was delayed until recovery to normal values.

All patients received chemotherapy as long as response was continued or for a total of two courses beyond the development of a complete disappearance of disease; stable disease after two courses of chemotherapy allowed the attending physician to continue treatment at his discretion.

Patient evaluation

Patients were assessed initially by a multidisciplinary team consisting of a medical oncologist, a radiation oncologist and a head and neck surgeon. Standard clinical, radiological and endoscopic examinations were performed to determine the indicator lesion(s).

The guidelines proposed by the WHO [8] and by Miller *et al.* [9] were adopted for the evaluation of response and toxicity.

A complete response was defined as the disappearance of all clinically detectable disease and a partial response as a > 50% reduction in the product of the greatest perpendicular diameters of all measurable lesions. To qualify as a responder, the patient had to fulfill the criteria in two subsequent monthly follow-up visits. Patients were assessed for response separately by the medical team administering the treatment and subsequently by the surgeon. The surgeon was unaware of the treatment regimen administered to the individual patients and when a disagreement on response occurred, consultation was required for a final decision.

During therapy, patients were seen at intervals dictated by the chemotherapy schedule. Following completion of all treatment, patients were followed at monthly intervals by the multidisciplinary team.

Table 1. Patients' characteristics

	Total	EMB	DMB
Median age	54	52	54
Range	(33–68)	(33–65)	(35–68)
Males/females	63/17	40/13	23/4
Median Karnofsky performance score	70	70	70
Range	(50–90)	(50–90)	(50–80)
Initial disease			
Larynx	22	15	7
Hypopharynx	15	10	5
Oropharynx	20	12	8
Oral cavity	21	14	7
Rhinopharynx	2	2	0
Initial treatment			
Surgery alone	3	1	2
RT alone	20	14	6
Surgery + RT	36	24	12
CT + locoregional	21	14	7
Present disease			
Primary	21	13	8
Lymph-node (lfn)	28	18	10
Primary + lfn	17	12	5
lfn + distant	13	9	4
Distant alone	1	1	0
No response/ Early relapse	40	26	14
Late relapse	40	27	13

CT = chemotherapy; RT = radiotherapy.

RESULTS

Patients

80 patients were registered (53 in arm A and 27 in arm B) and all are considered evaluable for analysis, regardless of the amount of treatment received (Table 1).

Treatment allocation by strata is shown in Table 2.

Prior treatment was surgery alone in 3 cases, radiotherapy alone in 20, surgery plus radiotherapy in 36; chemotherapy with DDP-5FU was delivered before radiotherapy (surgery) in the remaining 21 cases. The extent of disease at presentation for this trial was locoregional except in one case with distant metastases only (Table 2).

Table 2. Treatment allocation by strata (EMB: DMB = 2:1)

	No response or early relapse*	Late relapse*
No previous chemotherapy	18 EMB; 10 DMB	21 EMB; 10 DMB
Previous chemotherapy†	8 EMB; 4 DMB	6 EMB; 3 DMB

*To/after initial treatment; †Cisplatin + 120 h 5-Fluorouracil.

Table 3. Activity of EMB (53 patients) and DMB (27 patients) regimens

	EMB			DMB		
	No.	%	(C.I.)	No.	%	(C.I.)
CR	9	16		2	7	
PR	14	26		7	26	
OR total	23	43	(30–56)	9	33	(15–51)
OR previous CT*	5	36	(11–61)	0		
OR no previous CT*	18	46	(30–62)	9	45	(23–67)
SD	17	32		6	22	
PD	10	19		11	40	
NE	3	5		1	3	
OR duration in weeks	12			5		
range	(4–39)			(4–13)		

*Cisplatin + 120 h 5-Fluorouracil, CR = complete response, PR = partial response, OR = overall response, SD = stable disease, PD = progressive disease, NE = not evaluable, C.I. = confidence interval.

Response to EMB

16 patients were classified as responders after the first (37 patients) stage and therefore the second stage was started.

The accrual was terminated at the time of evaluation of the 23 responders and the alternative hypothesis was accepted.

The 53 patients randomised to arm A received 172 cycles of EMB (median: three cycles/patient; range 0–8). 3 patients in this group refused treatment after randomization and before therapy; as stated above, they were however included in the analysis.

Nine complete and 14 partial responses were observed (overall response rate = 43% ± 13), lasting a median of 12 (range 4–39) weeks. Five out of 23 remissions (1 complete and 4 partial) occurred among patients resistant to (3) or relapsing after (2) first line treatment inclusive of cisplatin plus 120 h 5-fluorouracil infusion.

The overall response rate by the prior treatment was 36% ± 25 (5/14 patients) for the previous chemotherapy group.

Table 3 summarises the therapeutic results of EMB regimen.

Acute toxicity of EMB

Acute toxicity of EMB regimen was considered acceptable (Table 3). Among observed WHO grade 2 or more, haematological complications were observed in 47% of patients (1 patient discontinued treatment because of a white blood cell count of 600/mm^3), oral mucositis in 42%, vomiting in 7%, fever in 8%; cutaneous toxicity (ulcers apart from the site of injection or neoplastic disease) was recorded in 10% of cases.

Table 4. Acute toxicity of EMB and DMB regimens (proportion of evaluable patients)

	WHO grade			
	1	2	3	4
	EMB/DMB (%)	EMB/DMB (%)	EMB/DMB (%)	EMB/DMB (%)
Haematological				
Haemoglobin	11/8	15/8	7/–	–/–
White cells	15/–	23/8	5/8	4/–
Platelets	–/–	2/–	–/–	–/–
Oral mucositis	15/8	19/16	23/8	–/4
Nausea/vomiting	7/12	5/16	2/25	–/–
Fever	19/–	4/8	4/8	–/–
Renal	–/12	–/8	–/–	–/–

Result of DMB regimen

Sixty-seven courses of DMB were administered to the 27 patients randomised to arm B (control group), with a median of two cycles/patient (range: 0–5).

9 out of 27 (33% ± 18) patients had a major response (2 complete and 7 partial responses), with a median duration of 5 (range 4–13) weeks.

None of the 7 patients previously treated with chemotherapy achieved a response with DMB. The response rate for patients with no prior chemotherapy was 45% ± 22 (9/22 patients).

6 patients had a stabilisation and 6 had progression of disease. 1 patient refused DMB after randomisation and before therapy.

5 patients refused to continue therapy after the first cycle of DMB (due to vomiting in 2, oral mucositis in 1, and unknown reasons in 2); they were considered as non-responsive.

Vomiting and oral mucositis were the main treatment-limiting side effects in this group, having been observed in 53% and 36% of patients, respectively.

Haematological toxicity was infrequent (16% WHO grade > 2 leucopenia) and renal toxicity episodic (2 cases WHO grade > 2). A fever > 38.5°C was observed in 16% of cases.

DISCUSSION

In patients with squamous cell head and neck cancer relapsing after loco-regional treatment, the DDP containing regimens showed response rates between 40% and 60%, irrespective of dose employed, schedule or modality of drug delivery [1, 2]. Even, if a superior response rate was observed, no advantages were obtained in terms of response duration and survival over methotrexate or cisplatin alone in phase III randomised studies [1, 2, 10–18].

In previously untreated patients the DDP containing combinations regularly produce higher response rates, ranging from 60% to 90% with complete response rates between 20% and 60%. The combination of cisplatin and 120 h 5-fluorouracil continous infusion (DDP-5-FU), seems particularly effective and it is generally adopted in clinical trials involving untreated patients [1, 2, 19]. Up to now no defined survival advantages has been, however, shown by the introduction of chemotherapy in first line treatment [19].

It is to be noted that patients who fail first line chemotherapy for recurrent or disseminated disease, as well as patients relapsing after induction chemotherapy, rarely respond to any other single agent or combination [1].

Despite the limited value of chemotherapy in relapsing patients it seems important to test, in this subset of patients, new regimens with potentially low toxicity, as well as regimens potentially non-cross resistant with the DDP-5FU. The role of anthracyclines in head and neck cancer is not yet well defined. Doxorubicin produced an encouraging response rate (23%) in advanced patients [2, 19].

Preliminary reports on epirubicin suggested a good effectiveness (25% RR) with low toxicity making this drug suitable for combination schemes [19, 22, 23].

Frequently substantial differences occur between different groups in evaluating the same phase II agent (combination). This phase II study, in order to avoid patient selection bias,

involved a randomisation between the experimental combination (EMB) and a treatment known to have a well defined antitumour value (DMB). The use of a control group does not need to represent a large drain on the limited patient resource, since a 2:1 randomisation scheme is certainly adequate [7].

The objective of this phase II randomised study was to evaluate the activity of a new combination epirubicin, methotrexate and bleomycin (EMB) regimen in recurrent head and neck cancer. The tolerability of the EMB and the possible non-cross resistance to previous DDP-5FU were secondary objectives.

The control arm (DMB) was chosen because of its activity and mild toxicity [3] and because we were able to reproduce, in a previous phase II study with this combination, the response rates from the literature [24].

In this randomised phase II study the EMB regimen showed encouraging results. Out of 53 patients, 23 (43% ± 13) obtained a major response with a median response duration of 4 months and a median of 3 (range: 0–8) delivered courses. The toxicities were mild and mainly represented by mucositis.

This study was designed to include patients either untreated or previously treated with DDP-5FU in neoadjuvant setting. Interestingly, 5 out of 14 (36% ± 25) pretreated patients (3 initially resistant and 2 with a later relapse) responded to EMB, suggesting a possible non-cross-resistance between the two regimens, to be verified in larger studies.

Results in the control group confirmed those available from the literature, with 33% ± 18 response rate and a moderate to severe toxicity mainly confined to gastrointestinal complaints. A median of two (range: 2–5) cycles were delivered. No response in chemotherapy pretreated patients were observed. Whether or not cisplatin-including combinations are superior to non-cisplatin-including combinations remains, in our opinion, a controversial issue.

To our knowledge the only phase III studies addressing this question have been published by the EORTC and by SAKK [26, 28]. In both studies the two experimental regimens differed from the control regimens only in the presence or absence of cisplatin. In EORTC study methotrexate, bleomycin and vincristine with or without cisplatin and in the SAKK study methotrexate, bleomycin, hydroxyurea with or without cisplatin were compared (i.e. a three vs. four drug combination).

In both studies the response rate of cisplatin containing regimens was significantly superior to that of the control regimens: 50% vs. 28% and 66% vs. 27%.

In our study we tested a new regimen including methotrexate and bleomycin combined with a drug like epidoxorubicin that showed in a series of phase II studies an activity of about 25% in head and neck squamous cell cancer [19, 22, 23]. A similar activity of about 25% has been shown by cisplatin when used alone [10–13, 18, 25, 27].

This study suggests that epirubicin, methotrexate and bleomycin combination, in recurrent head and neck cancer, produces result similar to cisplatin-containing regimens, with a mild toxicity and a good compliance and seems non-cross-resistant with a cisplatin plus fluorouracil combination. We believe these results are promising enough to justify a larger phase III study.

1. Vogl SE. Chemotherapy of recurrent and metastatic head and neck cancer In Vogl SE, ed., *Head and Neck Cancer*. New York, Churchill Livingstone, 1988, 65–77.
2. Al Sarraf M. Head and neck cancer: chemotherapy concepts. *Semin Oncol* 1988, **15**, 65–67.
3. Kaplan BH, Schoenfeld D, Vogl SE, *et al.* Treatment of recurrent (REC) or metastatics (MET) squamous cell cancer of head and neck (SCH&N) with methotrexate (M), plus diamminedichloroplatinum (D): a prospective randomized trial of the Eastern Cooperative Oncology Group. *Proc Am Assoc Cancer Res* 1981, **22**, 532.
4. Vogl SE, Schoenfeld DA, Kaplan BH, *et al.* A randomized prospective comparison of methotrexate with a combination of methotrexate with a combination of methotrexate, bleomycin and cisplatin in head and neck cancer. *Cancer* 1985, **56**, 432–442.
5. Paccagnella A, Cavaniglia G, Zorat PL, *et al.* Chemotherapy (CT) before locoregional treatment (LRT) in stage III + IV head and neck cancer: intermediate results of an ongoing randomized phase III trial. *Proc Am Soc Clin Oncol* 1990, **9**, 173.
6. Simon R. How large should a phase II trial of a new drug be? *Cancer Treat Rep* 1987, **71**, 1079–1085.
7. Peto R. Clinical trial methology. *Biomedicine* 1978, **28**, 24–36.
8. WHO handbook for reporting results of cancer treatment. WHO offset publication No 48, 1979, WHO Geneva.
9. Miller AB, Hoogstraten B, Staquet M, *et al.* Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
10. Campbell JB, Dorman EB, McCormick J, *et al.* A randomized phase III trial of cisplatinum, methotrexate, cisplatinum + methotrexate and cisplatinum + fluorouracil in end stage head and neck cancer. *Acta Otolaryngol* (Stockh)1987, **103**, 519–528.
11. Clavel M, Cappelare P, Cognetti F, *et al.* Comparison between C (Cisplatin) alone, two cisplatin containing multiple drug regimens: CABO (cisplatin, methotrexate, bleomycin, oncovin), and CF (Cisplatin-FU) in advanced head and neck carcinomas. Report on an randomized EORTC trial 24842 including 380 patients. *Cancer Chemother Pharmacol* 1989, **23** (suppl 2), c73 (A292 S).
12. Jacobs C, Lyman G, Velez-Garcia E, *et al.* Comparison of infusional 5-fluorouracil (5FU) and cisplatin (CDDP) in combination and as single agents for recurrent and metastatic head and neck cancer. *Proc Am Soc Clin Oncol* 1988, **7**, 154.
13. Jacobs C, Meyers F, Hendrickson C, *et al.* A randomized phase III study of cisplatin with or without methotrexate for recurrent squamous cell carcinoma of the head and neck. *Cancer* 1983, **52**, 1563–1569.
14. Williams SD, Velez-Garcia E, Essessee I, *et al.* Chemotherapy for head and neck cancer: Comparison of cisplatin plus vinblastine plus bleomycin versus methotrexate. *Cancer* 1986, **2**, 18–23.
15. Amrein PC. Cisplatin and 5-fluorouracil vs the same plus bleomycin and methotrexate in recurrent squamous cell carcinoma of the head and neck. *Proc Am Soc Clin Oncol* 1990, **9**, 175.
16. Drelichmann AI, Cummings G, Al-Sarraf M. A randomized trial of the combination of cis-platinum, oncovin and bleomycin (COB) versus methotrexate in patients with advanced squamous cell carcinoma of the head and neck. *Cancer* 1983, **52**, 399–403.
17. Eisenberger MA, Krasnow S, Silva H, *et al.* A comparison of carboplatin plus methotrexate versus methotrexate alone in patients with recurrent and metastatic head and neck cancer. *J Clin Oncol* 1989, **7**, 1341–1345.
18. Mortin RP, Stell PM. Cytotoxic chemotherapy for patients with terminal squamous carcinoma- does it influence survival? *Clin Otolaryngol* 1984, **9**, 175–180.
19. Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: De Vita VT jr, Hellman S, Rosenberg SA (eds), *Cancer Principles and Practice of Oncology*. Philadelphia, JB Lippincott, 1989, 488–590.
20. Magee MJ. Howard J, Bosl GJ, *et al.* Phase II trial of 4-epidoxorubicin in advanced carcinoma of the head and neck origin. *Cancer Treat Rep* 1985, **69**, 125–129.
21. Karpovsky B, Karp D, Vaughan C. A phase II randomized trial of weekly versus every 3 weeks epidoxorubicin in advanced squamous cell cancer of the head and neck. *Proc Am Soc Clin Oncol* 1987, **6**, 514.
22. Robustelli della Cuna R, Preti P, Cuzzoni Q. Epirubicin plus cisplatinum in the treatment of advanced head and neck cancer. In Bonadonna G, ed., *Advances in Anthracycline Chemotherapy: Epirubicin*. Milano, Masson 1984, 155.
23. Cersosino RJ, Hong WK. Epirubicin: a review of pharmacology, clinical activity and adverse effects of an adriamycin analogue. *J Clin Oncol* 1986, **4**, 425–439.
24. Paccagnella A, Venturelli E, Cavaniglia G, *et al.* Cisplatin (DDP), bleomycin (BLM) and methtrexate (MTX) in advanced head and neck cancer. *Proc 2nd Eur Conf Clin Oncol* (Amsterdam) 1983, **4**, 14.
25. Hong WK, Schaefer S, Issell B, *et al.* A prospective randomized

trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. *Cancer* 1983, 52, 206–210.
26. Clavel M, Cognetti F, Dodion P, *et al.* Combination chemotherapy with methotrexate, bleomycin and vincristine with or without cisplatin in advanced squamous cell carcinoma of the head and neck. *Cancer* 1987, **60**, 1173–1177.
27. Davis S, Kessler W. Randomized comparison of *cis*-diamminedichloroplatinum versus *cis*-diamminedichloroplatinum, methotrexate and bleomycin in recurrent squamous cell carcinoma of the head and neck. *Cancer Chemother Pharmacol* 1979, 3, 57–59.
28. Abele R, Honegger HP, Grossenbacher R, *et al.* A randomized study of methotrexate, bleomycin, hydroxyurea with versus without cisplatin in patients with previously untreated and recurrent squamous cell carcinoma of the head and neck. *Eur J Cancer Clin Oncol* 1987, 23, 47–53.

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Phase II Study of Vindesine and Dacarbazine with or without Non-specific Stimulation of the Immune System in Patients with Metastatic Melanoma

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A single dose of dacarbazine (DTIC), followed by a 5-day intravenous infusion of vindesine (VDS) was administered every 3 weeks to 103 patients with metastatic melanoma. One half of the patients were randomised to receive intravenous methanol extraction residue (MER) of bacillus Calmette-Guarin (BCG) in addition to chemotherapy, on days 7 and 14 of each course. 98 patients were evaluable. The response rates in treatment groups were 16 and 17%, respectively (confidence interval 9–24%). Neither the response rate nor the survival improved when MER was added to chemotherapy. Toxicity was moderate except for a significant granulocytopenia. The combination of DTIC and VDS is not more effective than DTIC alone and has added neurotoxicity.
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INTRODUCTION

DESACETYL VINBLASTINE amide sulphate or vindesine (VDS) is a synthetic vinca alkaloid derived from vinblastine sulphate, with a spectrum of experimental antitumour activity similar to vincristine [1]. Phase II studies of this agent for stage IV malignant melanoma have shown response rates varying from 0 to 35% [2–8]. The continuous 5-day infusion has been shown to be significantly superior to the single weekly administration schedule with less overall toxicities [9–11]. Dimethyl triazeno imidazole carboxamide (DTIC) or dacarbazine is the single most effective agent against melanoma with a response rate of 20 to 25% and a median survival of 4 months [12]. So far, combinations of DTIC with various antitumour agents have not yielded better therapeutic results than treatment with DTIC alone [13–14]. The most commonly used schedule of DTIC has been 250 mg/m^2/day × 5 every 3–4 weeks. However, studies with high-dose DTIC once a month have given similar response rates with less toxicity, particularly gastrointestinal side-effects [15–16]. In this phase II study we evaluated the efficacy and safety of a combination of high-dose DTIC followed by continuous 5-day infusion of VDS in 103 patients with metastatic malignant melanoma.

Methanol extraction residue (MER) of bacillus Calmette-Guerin (BCG) which has an acceptable toxicity consisting of fever, chills and rare pulmonary infiltrates when administered intravenously [17], has been shown to have significant antitumour activity against murine tumour models [18]. Some evidence of antitumour activity was also observed in phase I studies [19–21] and with intra-lesional treatments [22–24]. Its biological effects can be monitored by *in vitro* assays including antibody-dependent cytotoxicity (ADCC) [25]. Since the use of BCG in patients with melanoma has been associated with some beneficial effects, there was hope that intravenous administration of MER may have superior therapeutic effects. In order to further evaluate the role of non-specific stimulation of the immune system, the patients were randomised to receive either chemotherapy alone or additional therapy with MER intravenously on days 7 and 14 of each cycle of chemotherapy.

PATIENTS AND METHODS

Patients of both sexes, aged 15 or more, with histologically confirmed diagnosis of metastatic melanoma not amenable to surgery, were eligible to enter this study, provided they fulfilled the following conditions. Informed consent was required from each patient. The lesions evaluated for response to therapy had to be measurable (measures of two perpendicular diameters) or evaluable (measure of the biggest diameter). They had to be appropriately documented and surveyed by diagnostic procedures when necessary. Patients were expected to have a life expectancy of at least 12 weeks. They had to be put off all

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